

Functional Diagnosis of Hibernoma by FDG Imaging Under Propranolol Treatment: A Case Report

Bongioanni F¹, Pomposelli E², Pennone M², Fiz F¹, Cittadini G³, Ratto GB⁴, Morbelli S², Marini C⁵ and Sambuceti G^{1,2}

¹Nuclear Medicine Unit, Dept of Health Sciences, University of Genoa, IRCCS San Martino- IST, Genoa, Italy

²Nuclear Medicine, IRCCS San Martino IST-Genoa, Italy

³Radiology Unit, IRCCS San Martino- IST, Genoa, Italy

⁴Thoracic Surgery Unit, IRCCS San Martino- IST, Genoa, Italy

⁵CNR Institute of Bioimages and Molecular Physiology, Milan, Section of Genoa, Italy

Abstract

Positron Tomography/Computer Tomography (PET/CT) imaging of 18F-Fluorodeoxyglucose (18F-FDG) uptake is frequently used to recognize malignant nature of abnormal findings at anatomical investigations. However, several benign structures can mimic cancer glucose avidity. This case report pertains to a large mediastinal mass, incidentally detected on a coronary Computer Tomography (CT) study and showing heterogeneous signal hyperintensity in T1-weighted sequences at a subsequent Magnetic Resonance Imaging (MRI). CT-guided biopsy failed to provide adequate specimen; 18F-FDG PET/CT documented an extremely high glucose analogue consumption (maximum Standardized Uptake Value: 29). In order to exclude every alternative possibility before attempting a potentially hazardous surgery, we hypothesized the possible presence of a hibernoma. To test this hypothesis, we verified the influence of sympathetic innervation on lesion uptake, by repeating 18F-FDG imaging under beta-blockade: this scan documented the complete disappearance of the anomalous tracer uptake. A 6-months follow-up scan documented stable lesion volume and persistently absent 18F-FDG uptake under the beta-blockers, thus presumably excluding the malignant nature of the increased tracer uptake.

Keywords: Mediastinal mass; FDG; PET/CT; Hibernoma

Abbreviations: PET/CT: Positron Tomography/Computer Tomography; FDG: ¹⁸F-Fluoro-deoxyglucose (FDG); CT: Computed Tomography; MRI: Magnetic Resonance Imaging; SUV: Standardized Uptake Value

Introduction

The high glucose consumption typical of almost all solid tumors (the so called "Warburg effect") represents the basis for PET/CT imaging of ¹⁸F-Fluorodeoxy-glucose (FDG) uptake in cancer diagnosis and staging [1]. This technique became a standard in clinical oncology; nevertheless, its diagnostic accuracy is hampered by a low, yet significant, number of false positive findings. In fact, high FDG retention can be observed in benign lesion originating from tissues characterized by high glycolytic rate. This finding frequently occurs in benign neoplasms originating from brown fat, defined as "hibernomas", whose low prevalence (1.6% of benign lipomatous tumors) often prevents a correct identification [2-4]. Actually, these lesions are most frequently observed in areas occupied by brown persists after fetal life (mediastinum, retroperitoneum, as well as paravertebral, supra-clavicular and latero-cervical spaces) [5]. However, connective-tissue-derived malignant neoplasms (liposarcoma or high-grade rhabdomyosarcoma) can often originate in these same sites challenging the diagnostic accuracy of FDG uptake and morphological features interrogated by MRI or X ray CT. On the other hand, even histological or cytological evaluation is often hampered by the difficult approach for fine-needle aspiration cytology or excisional biopsy. In the present report, we describe a case report in which malignant fat-derived lesion was noninvasively excluded using a pathophysiological approach.

Case Report

A 75-year-old patient was referred to our institution for the metabolic characterization of a large mass in the upper anterior mediastinum, incidentally detected during a Computer Tomography (CT) coronary angiographic study. The study had been executed due

to previous detection of ascending aorta ectasia, in a patient affected by several cardio-vascular risk factors (hypertension, diabetes, history of smoking, obesity). At that time the patient was under active treatment with calcium channel blockers, aspirin and metformin but not with beta-blockers.

CT images displayed a scarcely defined mass, with heterogeneous densitometric values within the fat range that presented inhomogeneous contrast enhancement (Figure 1A). Subsequent MRI demonstrated mixed high signal intensity in T1-weighted sequences, mild hyperintensity in T2, and a heterogeneous signal loss in fat-suppressed acquisitions. The lesion displayed only mild mass effect on the surrounding structures (Figure 1B-C). CT-guided biopsy was then attempted but did not provided adequate specimen [6].

In this context, presence of malignancy couldn't be excluded and the patient was referred to FDG PET/CT scan. Image acquisition was performed 50 minutes after administration of 5MBq of 18F-FDG per Kg of patient weight. At tracer injection, the patient was fasting since 12 hours and lying in a recumbent position in a quiet room with an adequate temperature. Scan was performed using a 3D whole-body PET scan and a non-diagnostic CT scan protocol, for attenuation correction and anatomical localization. These parameters were used in all subsequent studies. The study demonstrated an extremely high tracer uptake within the mass (maximum SUV of 29), without any other

***Corresponding author:** Francesca Bongioanni, Nuclear Medicine Unit, Dept of Health Sciences, University of Genoa, IRCCS San Martino- IST, Genoa, Italy, Tel: 3901020991; E-mail: bongioannifrancesca@virgilio.it

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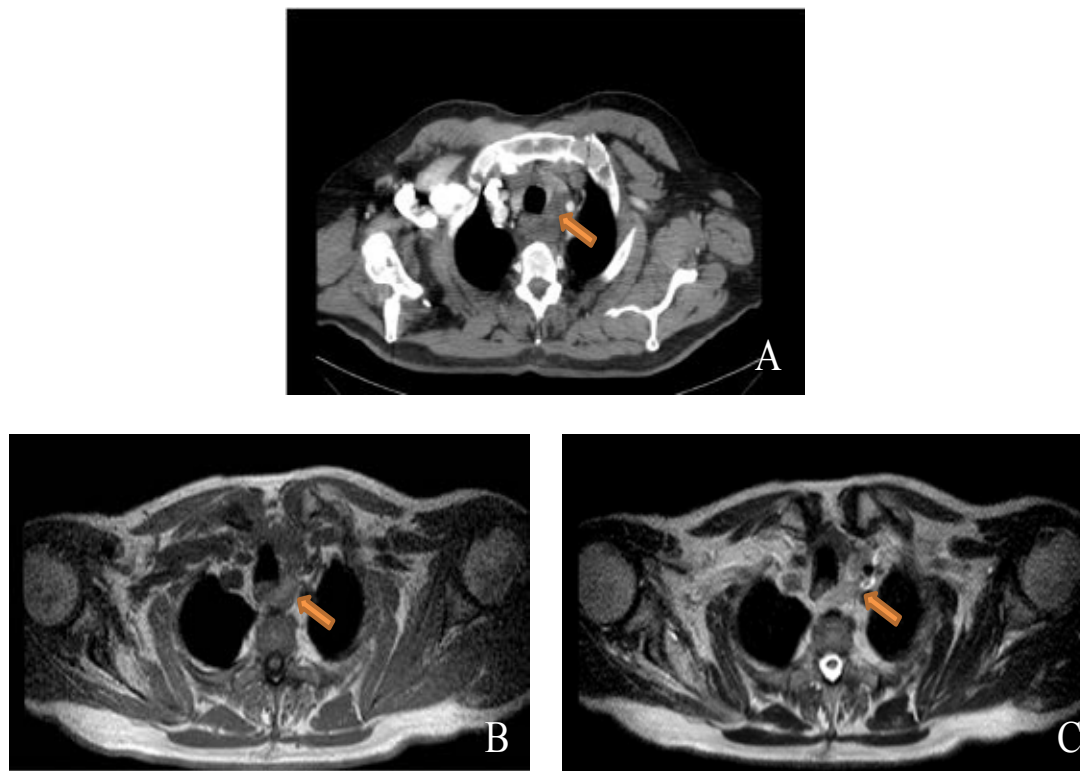


Figure 1: CT scanning and MRI study show a mediastinal mass.

A: CT coronary angiographic study highlights a lesion with distribution of densitometric values prevalently located within the fat range. This mass, located on the left paratracheal groove, shows a highly heterogeneous contrast enhancement pattern. Magnetic resonance imaging demonstrate a mixed high signal intensity in T1-weighted sequences **(B)**: Mild hyperintensity in T2 **(C)** With a heterogeneous signal loss in fat suppressed acquisition sequences.

anomalous findings (Figure 2A). This finding suggested a malignant nature of the lesion. Nevertheless, anatomical site did not permit to exclude a hibernoma mostly because the scan was performed during an extremely cold winter, possibly triggering adrenergic stimulation of brown fat glucose consumption.

Accordingly, lesion nature remained undefined while its surgical excision entailed a considerable procedural risk, owing to mass size and relationships with both esophagus and left carotid artery. To justify the hazard related to surgery we thus planned to characterize the pathophysiological mechanisms underlying the high FDG uptake. To this purpose we planned to verify whether the intense glucose consumption was related to adrenergic activation by repeating PET/CT scanning under full dose beta-blocker therapy [7-9]. Repeated study, under propranolol treatment (120 mg per day, starting 5 days before the exam) documented the virtual disappearance of FDG uptake within the lesion, with a SUV max of 1.1 (Figure 2B).

This finding was interpreted as a marker of a benign lesion nature and indicated a strategy shift from the possible surgical option to a close follow up program that implied to repeat PET/CT scan after 6 months. The study was performed under the same propranolol treatment regimen and confirmed the absence of FDG uptake (SUV max 0.9) within the lesion that moreover, displayed the same volume at coregistered CT images (Figure 2C).

Discussion

Hibernoma is a rare asymptomatic and benign lesion. Its diagnostic

definition is hampered by the lack of morphologic criteria able to accurately differentiate this rare incidental from other malignant lesions such as liposarcoma, rhabdomyosarcoma, giant cell tumor and lymphoma [6,10-12]. A similar misdiagnosis can occur at PET/CT imaging since the high FDG intake can reflect either a Warburg effect of a rapidly proliferating high-grade mesenchymal tumors and a high glycolytic flux caused by adrenergic activation of brown fat to preserve body temperature under cold exposure. Accordingly, this differential diagnosis most often asks for cytological or histological evaluation [13,14].

Actually, brown fat behavior reflects the integrated response against intense cold, which is mediated by the adrenergic system and comprises vasoconstriction (Alpha-1 receptors), shivering (Beta-2 receptors) and, especially in infants and young adults, stimulation of heat production by the brown adipose tissue (Beta-3 receptors). Hibernomas are benign, well differentiated lesions, and maintain the functional characteristics of the original tissue. In patients submitted to PET/CT in winter, the accelerated glucose metabolism can simulate malignant lesions at FDG PET/CT imaging [14]. Yet, the physiological regulation of this metabolic pattern, and thus the benign nature of the tissue can be documented by pharmacologic interventions able to reduce tracer retention in physiological brown tissue [7-9].

This case presents an unusual sequence of diagnostic test planning in which the functional study permitted to define an otherwise uncertain diagnosis. The complete first-line workup strongly suggested a malignant lesion and the need for a potentially hazardous surgical

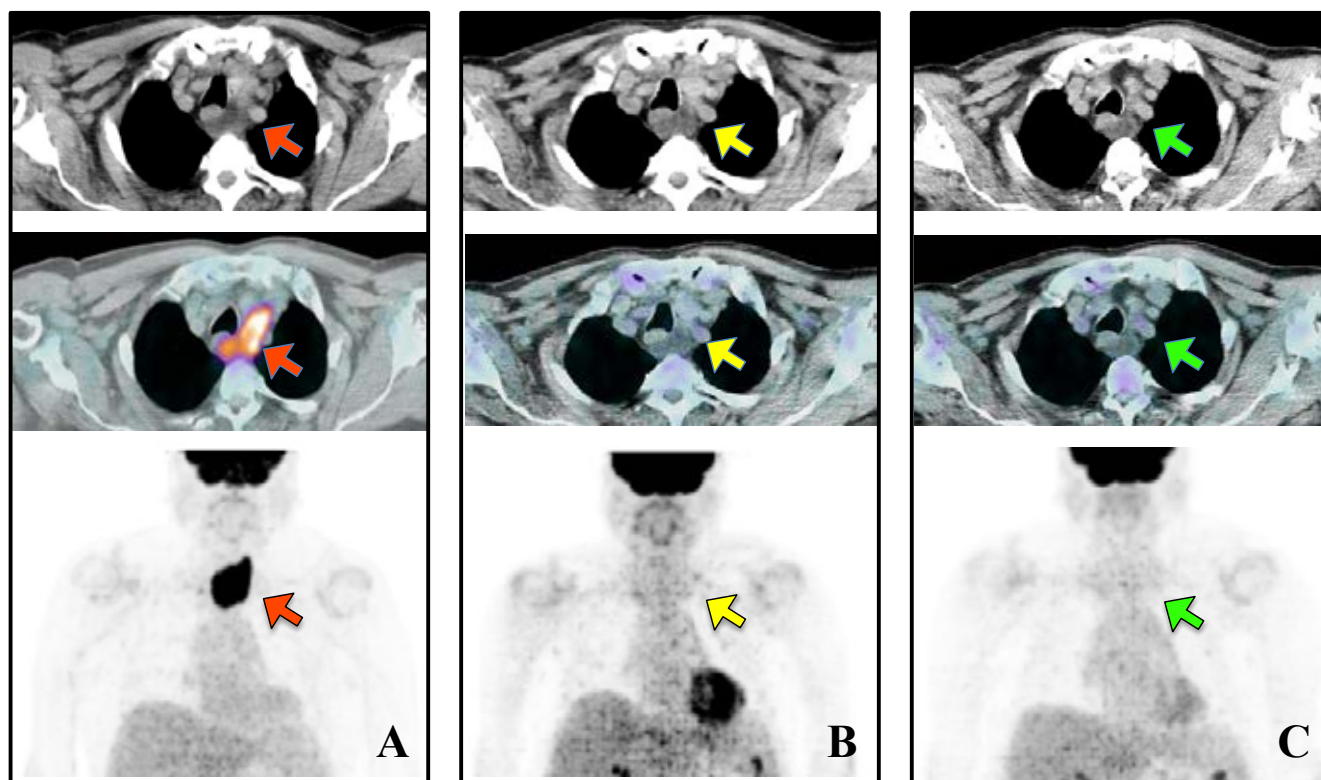


Figure 2: PET/CT scans: baseline imaging and after treatment with beta-blockers.

A: Baseline 18F-FDG PET/CT scan shows an extremely high FDG uptake within the mediastinal mass (SUV max 29) suspicious for hypermetabolic malignant lesion.

B: PET/CT scan after five days of treatment with propranolol (120 mg/die) demonstrate a complete disappearance of tracer hyperaccumulation within the mass.

C: PET/CT scan after six months, under the same treatment protocol, confirmed an absent FDG uptake within the lesion.

approach. The only non-invasive way to rule out this scenario was to consider the possible pharmacologic modulation of metabolic signal. To this purpose, we selected the unselective propranolol whose action on beta-3 receptors has been already documented [15,16], although the effectiveness of other beta-blockers was not tested. The inclusion of this possibility in the differential diagnosis and planning functional imaging procedures was, in this case, the key for this diagnosis.

There are of course several limitations intrinsic to this approach. First, the CT scanning protocol that is used in hybrid PET/CT imaging is “low dose”, for the sake of limiting the patients’ exposure to ionizing radiations, therefore limiting our anatomic definition of the lesion and its changes in follow-up scans. However, the complete metabolic response after beta-blockade, the absence of macroscopic modifications and the lack of local invasion or distant localizations at follow-up scans strongly support the hypothesis of a benign lesion [17,18].

Moreover, no further biopsies were attempted, given the inconclusive result of the first one. An excisional biopsy might theoretically have clarified the diagnosis, but the risk/benefit ratio was too high (also considering the negative follow-up imaging) to justify such an approach.

This report confirms the need of considering, planning and carefully interpreting functional imaging and decoding its meaning on the basis of the underlying pathophysiological mechanisms.

Consent

Written informed consent was obtained from the patient for publication of this Case Report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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Competing Interest

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